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| EXAMINER | |
|---|---|
| KERR, KATHLEEN M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 13 |

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/935,757 | MOCKEL ET AL. | |
| | Examiner | Art Unit | |
| | Kathleen M Kerr | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-8,17,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Application Status*

1. In response to the previous Office action, a written restriction requirement (Paper No. 10, mailed on June 4, 2003), Applicants filed an election received on July 9, 2003 (Paper No. 12). Claims 1-20 are pending in the instant Office action.

### *Election*

2. Applicants' election without traverse of Group II, Claims 9-16 and 18, in Paper No. 12 is acknowledged. Claims 1-20 are pending in the instant application. Claims 1-8, 17, and 19-20 are withdrawn from consideration as non-elected inventions. Claims 9-16 and 8 will be examined herein.

### *Priority*

3. The instant application is granted the benefit of priority for the foreign applications 10043336.7 and 10126422.4 filed in Germany on September 2, 2000 and May 31, 2001, respectively, as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are in German and cannot be used to establish an earlier effective filing date for the claimed subject matter.

The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/295,009 filed on June 4, 2001 as requested in the declaration. The subject matter of the pending claims is disclosed in the provisional application; thus, the effective filing date of the pending claims is June 4, 2001.

***Information Disclosure Statement***

4. The information disclosure statement filed on March 18, 2002 (Paper No. 8) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. The citation of the SR reference has been corrected by the Examiner; no action is required by Applicants. The VR reference (search report) was considered but is crossed out because this citation is not printed on the front of any patent that may evolve from the instant application.

***Compliance with the Sequence Rules***

5. By virtue of the sequence listing filed on December 6, 2001 (Paper No. 5), the instant application now fully complies with the sequence rules.

***Objections to the Specification***

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods of Making L-Amino Acids in Coryneform Bacteria using the SigE Gene---

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species, *Corynebacterium glutamicum,* for completeness.

8. The specification is objected to for lacking continuity data in the first paragraph. The instant application claims the benefit of U.S. Provisional Application No. 60/295,009 filed on June 4, 2001; however, no citation is noted in the first paragraph. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

9. The specification is objected to for the order of its content. The brief description of the drawings at the end of the specification should be moved to page 4, before "Detailed Description of the Invention". Correction is required.

10. The specification is objected to for being confusing. On page 6, line 20, the phrase "enzyme sigma factor E" is unclear as to what enzyme function this protein has. Limited description can be found in the specification and/or the art. Clarification is required.

***Objections to the Claims***

11. Claims 15 and 16 are objected to for having improper structure of a Markush group. At the end of the group list of Claim 15, between 15.13 and 15.14, an ---and--- is required. At the end of the group list of Claim 16, between 16.3 and 16.4, an ---and--- is required.

12. Claim 18 is objected for bring drawn to non-elected subject matter by virtue of its dependence on "one of more of the preceding claims" which includes non-elected Claims 1-8 and 17.

13. Claim 18 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel

the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The methods of Claims 9-16 all require the fermentation of coryneform bacteria, which is a synonym for the genus *Corynebacterium*. Thus, this limitation is already in the preceding claims.

***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 9-16 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of "**the** sigE gene of nucleotide sequences which code for it" (emphasis added) are unclear. The article "the" in many of the claims indicates a single gene, but which gene? Only one example of a sigE gene is described in the instant specification – that of *C. glutamicum* (SEQ ID NO:1 encoding SEQ ID NO:2). The specification discloses a single sequence defined as a sigE gene in SEQ ID NO:1, which encodes SEQ ID NO:2. This encoded protein is described as "an enzyme sigma factor E" on page 6 but no further explanation of this enzymatic activity is described in either the specification. The art contains a reference to sigE; however, the encoding DNA disclosed has little similarity to SEQ ID NO:1 (GenBank Accession Number U87307). Thus, if the claims were drawn to using enhanced SEQ ID NO:1 or any DNA encoding SEQ ID NO:2, the metes and bounds would be clear. If the claims are drawn to enhancement using any sigE gene, without clear definition of a sigE gene, the claims are wholly unclear.

Also, must the sigE gene that is enhanced be the endogenous *Corynebacterium* sigE gene of the cell claimed (if the cell is *C. glutamicum*, must enhancement be of a C. *glutamicum* sigE gene or can an sigE gene from *C. melassecola* be added to meet the limitations of the claim)?

Additionally, what are "nucleotide sequence which code for it"? Nucleotide sequences do not code for genes, they encode proteins. Thus, this phrase is wholly unclear.

Clarification on all the above points is required.

15. Claims 9-16 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "in particular overexpressed" in Claims 9 and 13 is unclear. The phrase renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See M.P.E.P. § 2173.05(d). Clarification is required.

16. Claims 10, 11, and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "biosynthesis pathway" and "metabolic pathways" are unclear as to their metes and bounds. The metes and bounds of the cited "pathways" are unclear so that the skilled artisan would be unable to identify enhancement (or reduction) of which additional genes reads on the claims. The specification cites only examples of genes to be turned on or off and do not define the pathways. Since coryneform bacteria have integrated, complex pathways of biosynthesis and degradation, the particular nature of the intended

additional genes is unclear without at least citation to a particular reference. Clarification is required.

17. Claims 14 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "regulatory properties of the polypeptide (enzyme protein) for which the polynucleotide sigE codes" is unclear. No regulatory properties are mentioned in the specification or the art. Moreover, is the regulation of the gene expression or of the polypeptide activity or both? Additionally the use of the parentheses is unclear. Clarification on all these issues is required.

18. Claims 15, 16, and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 15 and 16, the structure of "15.1, 15.2" is confusing because similar numbering is used for the claims. The Examiner suggests other list-defining items, such as a, b, c, or i, ii, iii. Correction is required.

19. Claims 15, 16, and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of phrases like "**the** dapA gene" (emphasis added) are unclear. The article "the" in many of the claims indicates a single gene, but which gene? Only one example of each of the listed genes, all from *C. glutamicum*, is described in the instant specification (see pages 12-14). Must the dapA gene that is enhanced be

the endogenous *Corynebacterium* dapA gene of the cell claimed (if the cell is *C. glutamicum*, must enhancement be of a C. *glutamicum* dapA gene or can a dapA gene from *C. melassecola* be added to meet the limitations of the claim)? Clarification is required.

20. Claims 15 and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "codes for lysine export" is unclear. Genes do not code for functions; genes codes for enzymes or proteins that have function. The appropriate phrase is ---the gene lysE coding for a protein for lysine export---. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 9-16 and 18 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 9 is drawn to methods of producing amino acids in coryneform having enhanced a sigE gene, wherein sigE is claimed solely by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a

precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the sigE gene is described as encoding "an enzyme sigma factor E" on page 6 but no further explanation of this enzymatic activity is described in either the specification or the art. A single example of a sigE protein is described in SEQ ID NO:2, but no indication of how this structure is related to the noted function (albeit an unclear function). Thus, one of skill in the art would be unable to predict the structure or function of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to methods using coryneform bacteria containing the genus of said genes are not adequately described.

22. Claims 9-16 and 18 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using coryneform bacteria with overexpressed sigE and/or amino acid biosynthetic genes and with deleted amino acid reduction genes, does not reasonably provide enablement for methods using bacteria with enhancement and/or elimination of pathways or attenuation of such genes. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To produce bacteria for use in the claimed methods to the full extent of the claimed scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification describes enhancement as increasing the copy number of a gene, using a strong promoter, or using a corresponding gene coding for an enzyme with a higher activity (see page 5). While the skill of the art enables enhancement by overexpression, which

would include increasing the copy number and using a strong promoter, of the disclosed sigE gene, no such enablement for using a corresponding gene coding for an enzyme with higher activity is found in the art. Furthermore, no activity of sigE is even known so that it can be increased using an altered protein form. The amino acid sequence of a sigE protein with higher activity is wholly unpredictable since no description of how the structure, SEQ ID NO:2, related to the function (albeit an unclear function). Thus, while the specification enables overexpression of the sigE gene (overexpression including means of art such as stronger promoters and increased copy number), it does not enable enhancement of said gene.

Similarly, the specification mentions in passing genes of the biosynthesis pathways of desired amino acids. The art contains numerous recitations of such genes and their enhancement by means of overexpression and alternate enzyme (more active enzyme) forms. The claims are enabled for such enhancements. However, where a more active enzyme form is not known in the art, such a form is wholly unpredictable from the art and the lack of any particular description in the instant specification.

Additionally, the elimination of biosynthetic pathways is a very complex procedure due to the intertwining of the multitude of biochemical pathways in coryneform. The specification enables methods that wholly delete said pathways so that the pathways are "switched off". Moreover, the specification enables methods using bacteria with deleted PEP carboxykinase genes (for example, as in Claim 16). However, the specification does not enable for alteration of the pathways so that they no longer reduce the formation of the desired amino acid using any means short of full deletion. Moreover, the specification does not enable attenuation of PEP carboxykinase, for example, by means other than deletion. The art contains numerous recitations

of such pathways and genes and their reduction by means of deletion and alternate enzyme (less active enzyme) forms. The claims are enabled for such reduction or attenuation methods. However, where a less active enzyme form is not known in the art, such a form is wholly unpredictable from the art and the lack of any particular description in the instant specification.

23. Claim 14 is rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Raising the regulatory properties of a sigE polypeptide for use in the claimed methods would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

Not only are regulatory pathways of the sigE polypeptide not described in the specification or known in the art, but also the normal activity of sigE polypeptides is not described. Without any indication of function, it is wholly unpredictable how a skilled artisan would be able to regulate such an activity. No guidance or working examples are offered in the instant specification. The state of the art is totally devoid of discussion of sigE polypeptide regulation. Thus, the instant claim is not enabled.

24. Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using known feedback-resistance aspartate kinase and threonine dehydratase, does not reasonably provide enablement for methods using unknown feedback-resistance aspartate kinase and threonine dehydratase. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Identifying novel feedback-resistance aspartate kinase and/or threonine dehydratase polypeptides for use in the claimed methods would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

The specification provides a single example of each of the named polypeptides but provides no guidance for the identification of new ones. The state of the art is such that a finite number of feedback-resistant aspartate kinases and threonine dehydratases are known; these are enabled. However, the predictability of finding other feedback-resistant aspartate kinases and threonine dehydratases is minute. Thus, the instant claim is not enabled to the full extent of its scope.

***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 9, 12, 13, and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kimura *et al.* (EP 0864654-see IDS). The instant claims are drawn to methods of making amino acids using coryneform bacteria that overexpress, via a plasmid vector, sigE and further isolating said amino acid.

Kimura *et al.* teach methods of making amino acids by overexpression of a gene encoding the sigma factor (see abstract and page 3, line 14). Without further clarity of the function of sigE in the instant specification, sigE is considered a sigma factor. Kimura *et al.* teach using plasmids in the methods (see page 6, example 1). Kimura *et al.* also teach coryneform as microorganisms for the disclosed methods (see page 3, line 22) and teach collection of the amino acids by known methods (see page 5, lines 49-51).

***Other Art of Note***

26. The following are comments on relevant art that is not available as prior art against the claimed methods.

a) Nakagawa *et al.* (EP 1108790 in IDS), which is not prior art based on the publication date of the PCT, teach methods of producing amino acids using transformants overexpressing all of the disclosed open reading frames therein and isolating said amino acids; they further teach *C. glutamicum* as host cells in said method (see page 4). Nakagawa *et al.* also teach lysine as preferred product of *Corynebacterium glutamicum* (see page 2). Nakagawa *et al.* teach a particular open reading frame similar to sigE in *M. smegmatis* that comprises a polynucleotide that is identical to the encoding portion of SEQ ID NO:1.
b) GenBank Accession Number U87307 (in IDS) teaches a *Mycobacterium smegmatis* sigE involved in survival following stress. No indication of its use in coryneform or for the production of amino acids is found in the art.

***Conclusion***

27. Claims 9-16 and 18 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
September 30, 2003